FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2013/2014

Rui Alexandre dos Santos Lopes

Diabetes and cardiovascular disease: is diabetes a risk equivalent?

março, 2014

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Rui Alexandre dos Santos Lopes

Diabetes and cardiovascular disease: is diabetes a risk equivalent?

Mestrado Integrado em Medicina

Área: Endocrinologia

Trabalho efetuado sob a Orientação de:
Dra. Maria Elisabete Gonçalves Rodrigues
E sob a Coorientação de:
Doutor Davide Maurício Costa Carvalho

Trabalho organizado de acordo com as normas da revista:
Revista Portuguesa de Cardiologia

março, 2014

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, Rui Alexandre dos Santos Lopes, abaixo assinado, nº mecanográfico 200802357, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 20/03/2014

Assinatura conforme cartão de identificação:

Rui Alexandre dos Santos Lopes

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

NOME

Rui Alexandre dos Santos Lopes

CARTÃO DE CIDADÃO OU PASSAPORTE (se estrangeiro)	E-MAIL	TELEFONE OU TELEMÓVEL
13491319	mimed08226@med.up.pt	912798532

NÚMERO DE ESTUDANTE	DATA DE CONCLUSÃO
200802357	20-03-2014

DESIGNAÇÃO DA ÁREA DO PROJECTO

Endocrinologia

TÍTULO ~~DISSERTAÇÃO~~/MONOGRAFIA (riscar o que não interessa)

Diabetes and cardiovascular disease: is diabetes a risk equivalent?

ORIENTADOR

Maria Elisabete Gonçalves Rodrigues

COORIENTADOR (se aplicável)

Davide Maurício Costa Carvalho

É autorizada a reprodução integral desta ~~Dissertação~~/Monografia (riscar o que não interessa) para efeitos de investigação e de divulgação pedagógica, em programas e projectos coordenados pela FMUP.

Faculdade de Medicina da Universidade do Porto, 20/03/2014

Assinatura conforme cartão de identificação: Rui Alexandre dos Santos Lopes

Ao meu padrinho

Diabetes and cardiovascular disease: is diabetes a risk equivalent?

Diabetes e doença cardiovascular: será a diabetes um equivalente de risco?

Rui Santos Lopes[a]; Elisabete Rodrigues[a;b]; Davide Carvalho[a;b]

[a]Faculdade de Medicina da Universidade do Porto, Porto, Portugal. [b]Serviço de Endocrinologia do Centro Hospitalar São João, Porto, Portugal.

Correspondência para autor:

Rui Alexandre dos Santos Lopes

Rua de S. Pedro, nº 101

4405-785 Madalena

Vila Nova de Gaia. Porto. Portugal

Email: ras_lopes@hotmail.com; mimed08226@med.up.pt

Número total de palavras do manuscrito: 4931

Resumo

Introdução e objetivos: A doença cardiovascular é causa importante de morbilidade e a principal causa de mortalidade em doentes diabéticos acarretando um aumento de risco 2 a 3 vezes para eventos cardiovasculares. O conceito de que a diabetes é um equivalente de risco cardiovascular surgiu na comunidade médica após a publicação de um estudo de cohort prospectivo, em 1998. Desde então foram publicados estudos que suportavam e outros que refutavam esta ideia. O objetivo deste artigo é rever a literatura publicada no últimos 5 anos e discutir o conceito de que diabetes é um equivalente de risco cardiovascular.

Métodos: Foi realizada uma pesquisa bibliográfica usando a PubMed, a Web of Science e a Scopus. Os artigos foram restritos aos últimos 5 anos, em inglês e português.

Resultados: Foram encontrados 16801 artigos, obtendo-se 20 artigos que foram usados nesta revisão.

Conclusões: A Diabetes, por si só, não deve ser considerada um equivalente de risco cardiovascular. A avaliação de risco deve incluir parâmetros como hemoglobina glicada, glicemia em jejum e duração da doença. Esta mudança de paradigma tem implicações clínicas, nomeadamente a restrição da utilização de estatinas nos doentes de risco mais baixo.

Palavras-chave: diabetes, glicemia, glucose, HbA1C, risco cardiovascular, risco de doença coronária.

Abstract

Introduction and Aim: Cardiovascular disease is an important cause of morbidity and the most important cause of mortality in diabetic patients with a 2-3 fold increased risk of cardiovascular events. The concept that diabetes is a cardiovascular disease equivalent arose in the medical community after Haffner's study in 1998. Since then studies supporting and refuting this principle were published. The aim of this paper was to review literature in the past 5 years and discuss the concept of diabetes as a cardiovascular disease equivalent.

Methods: Literature research was performed using PubMed, Web of Science and Scopus. Articles were restricted to the last 5 years and to English and Portuguese languages.

Results: 16801 articles of were found during research. After exclusion, 20 articles remained and were used in the conception of this review.

Conclusions: Diabetes *per se* should not be considered a cardiovascular disease equivalent. Risk assessment tools should focus on parameters like glycated haemoglobin levels, FPG levels and duration of the disease. This change of paradigm has clinical implications such as restricting the use of statins in lower risk groups.

Keywords: diabetes, glycemia, glucose, HbA1C, cardiovascular risk, coronary heart disease risk.

Abreviaturas

ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
apoB/apoA	Apolipoproteina B/apolipoproteina A
CHD	Doença coronária
CKD	Doença renal crónica
CVD	Doença cardiovascular
DM	Diabetes Mellitus
FMD%	Percentagem de dilatação fluxo-mediada
HbA1c	Hemoglobina glicada
IFG	Glicemia em jejum anormal
MI	Enfarte do miocárdio
NGT	Tolerância à glicose
SDDM	DM detectada
SRDM	DM reportada
T1D	DM tipo 1
T2D	DM tipo 2

Abbreviations

ADVANCE	Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation
apoB/apoA	Apolipoprotein B/apolipoprotein A
CHD	Coronary heart disease
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DM	Diabetes Mellitus
FMD%	Percentage of flow mediated dilatation
HbA1c	Glycated haemoglobin
IFG	Impaired fasting glucose
MI	Myocardial Infartion
NGT	Normal glucose tolerance
SDDM	Screen-detected DM
SRDM	Self-reported DM
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus

Introduction

Cardiovascular disease (CVD) is an important cause of morbidity and the most important cause of mortality in diabetic patients[1, 2] accounting for more than 70% of the deaths[2]. Studies have shown that DM is associated with a two to three fold increased risk of cardiovascular events (CVE)[1, 3]. In 1998, Haffner et al has shown that people with type 2 DM without a prior myocardial infarction (MI) have similar risk of coronary heart disease (CHD) as non-diabetics with a previous MI[4], suggesting that DM is a CVD risk equivalent. This study had considerable impact in the medical community in terms of intensive prevention of CHD in people with DM[4]. However, the concept of DM as a CVD equivalent has been questioned and, since then, papers supporting his findings[5, 6] and papers who did not[7-9] were published. In the face of this dissent, the aim of this paper is to review the published literature in the past 5 years and discuss the concept of DM as a CVD equivalent.

Methods

Search strategy

Literature research was performed using PubMed, Web of Science and Scopus on September 8th 2013 using the following query: (diabetes AND "cardiovascular risk") OR (glycemia AND "cardiovascular risk") OR (glucose AND "cardiovascular risk") OR (HbA1c AND "cardiovascular risk") OR (diabetes AND "coronary heart disease risk") OR (glycemia AND "coronary heart disease risk") OR (glucose AND "coronary heart disease risk") OR (HbA1c AND "coronary heart disease risk").

PubMed, Web of Science and Scopus researches were limited to the last 5 years with language restriction to English and Portuguese. Web of Science research was restricted to cardiovascular system and cardiology, endocrinology and metabolism, nutrition and dietetics, biochemistry and molecular biology and geriatrics and gerontology subject areas. Scopus research was restricted to following subject areas: Medicine, Nursing, "Pharmacology, Toxicology and Pharmaceutics", "Biochemistry, Genetics and Molecular Biology". No subject area restriction was applied to PubMed research.

Selection criteria

Articles were included if they: (1) were written in English or Portuguese; (2) contained at least one of the following keywords: diabetes, glycaemia, glucose, hbA1C; (3) and contained at least one of the following keywords: cardiovascular risk, coronary heart disease risk.

Articles were excluded if they were not inserted in cardiology, endocrinology nor metabolism subject areas. Articles whose aim was not cardiovascular or coronary heart disease risk assessment were excluded.

Data extraction

Titles and abstracts from the literature research were imported to Endnote X7®. Duplicates were found comparing title, authors and year of publication. After exclusion of duplicates, titles were reviewed, followed by abstract and full paper analysis. Articles whose abstracts or full text were not available were excluded.

Results

We found 16801 articles (PubMed: 6244; Web of Science: 8099; Scopus: 2458). After duplicate exclusion, 13124 articles remained and selection based on title alone was performed (Fig. 1); 12771 articles were excluded. Abstract selection was performed in 353 articles; 278 were excluded because abstract did not met the selection criteria and, 7 articles did not presented abstract at all. Subsequently full text selection was performed on 68 articles; 41 were excluded because full text did not met the selection criteria, 5 did not present full text available and 2 were excluded because were editorials. 20 articles remained and were used in the conception of this review.

Table 1 organizes and overviews the articles included in this review.

Discussion

The impact of Haffner's[4] study was undeniable. Despite its limitations and the lack of power to detect differences between two groups of patients[10], the concept that DM as CVD risk equivalent ingrained into medical community. This led institution of risk modifier drugs, namely statins, to reduce the risk. However, novel studies were published that questioned or refuted Haffner et al[4], leading to disagreement still today.

In this section, we are going to individually address each study found, dividing them in the following groups: studies supporting the hypothesis that DM is a CVD equivalent, studies refuting this hypothesis, studies that give no straight answer, and reviews

Studies supporting the hypothesis that diabetes is a cardiovascular disease equivalent

The article published by Berry C. et al (2010)[11] was the only study found in this research that clearly supported the hypothesis that DM is a CVD risk equivalent. In this clinical trial 426 patients were included; 53% (n=226) had normal fasting blood glucose, 28% (n=118) had impaired fasting glucose (IFG) and 19% (n= 82) had diabetes. These patients underwent coronary artery intravascular ultrasound at baseline and after a mean follow-up period of 664 days and were randomly assigned to one of three doses of avasimibe, a acyl-coenzyme A:cholesterol acyltransferase inhibitor, or to placebo. The study revealed that diabetic patients (73.33±8.86%) had greater maximum percentage coronary atheroma area at baseline than those with normoglycaemia (69.08±10.43%; p=0.001) and IFG (69.32±9.59%; p=0.0052) with no significant difference between normal and IFG groups. It was also shown a significant correlation between change in mean plaque area and change in mean lumen area in normoglycaemic and IFG partients but not in diabetics. Percentage atheroma volume was examined at baseline by quartiles of glycated haemoglobin (HbA1c) which has shown a significantly correlation (p=0.016) with percentage atheroma volume being higher in the highest quartile. FBG tended to correlate negatively with lumen volume at baseline (r=−0.09, p=0.066) and at follow-up (r= −0.09, p=0.083). This data indicates that: diabetic patients (vs normoglycemic and IFG group) had

greater coronary atheroma burden; atherosclerosis severity and coronary remodelling differed according to glycaemic status; and FBG and HbA1c were correlated with plaque burden, atherosclerosis progression and coronary remodelling. Authors refer that patients with HbA1c >10% were not included in this study, so the results may under-represent the magnitude of the diabetes-related effects on CHD.

Studies refuting the hypothesis that diabetes is a cardiovascular disease equivalent

In a 10-year prospective cohort study of 4410 patients, from Catalonia (Spain) Cano et al[12] recruited 2260 patients with type 2 diabetes (T2D) without coronary heart disease (CHD) and 2150 with first acute MI without diabetes. The authors compared long-term cardiovascular risk between T2D patients and first MI patients to assess the influence of diabetes duration, type of treatment, and glycaemic control at baseline. They found that the incidence rate for all cause death, coronary death, cardiovascular mortality, fatal and non-fatal MI and coronary heart disease were significantly worse among patients who survived acute, except for stroke death and unstable angina. These differences held after adjustment for potential confounders. It was shown that duration of diabetes was a determinant of cardiovascular outcomes (cut point at 8 years of disease duration) and patients with HbA1c ≥7% had worse prognosis.

Saely CH et al (2010)[13] recruited 756 consecutive patients referred to routine coronary angiography between October 1999 and October 2000 and recorded the vascular events over 4 years to investigate the contribution of baseline coronary atherosclerosis to the risk of diabetic patients for future CVE. At baseline angiography, 244 had neither T2D nor significant CHD, 50 had T2D but not significant CHD, 342 had significant CHD but no TD2, and 114 had both T2D and significant CHD. It was verified higher incidence of vascular events among patients with T2D than among non-diabetics (32.3vs.18.3%; $p<0.001$) and higher incidence of CVE among patients with significant CHD compared when compared with those without (29.4vs.8.8%; $p<0.001$). Presence of significant CHD at baseline conferred a higher vascular risk (adjusted HR= 3.46; $p<0.001$) than the presence of T2D (adjusted HR= 1.55; $p=0.021$). CVE were similar in T2D patients without significant CHD vs non-diabetics without significant CHD, but higher in non-

diabetics with significant CHD (p<0.001) and highest in patients with both, T2D and CHD (p<0.001). T2D patients without CHD had a significantly lower event rate than non-diabetic patients with significant CHD (p=0.008). The authors concluded that baseline coronary artery state determines vascular risk in patients with T2D patients and diabetes was not a CHD risk equivalent, though vascular risk was higher in the overall sample of T2D patients than in CHD patients.

In a prospective cohort study, Paynter NP et al (2011)[14] followed a total of 24 674 women (685 diabetics) and 11 280 men (563 diabetics) aged <80 years. The median follow up were 10.2 years and 11.8 years for women and men, respectively. The aim of this study was to generate CVD risk models that included HbA1c levels and compare its predictive ability with classification based on current guidelines for the diabetic participants; it was also examined the effect of a dichotomous term for diabetes in place of HbA1c levels. The authors demonstrated on both cohorts of men and women that measurement of HbA1c level in diabetic subjects improved risk prediction compared with classification of DM as CVD risk equivalent but with improved risk prediction in the women cohort. The authors also verified that diabetes alone did not confer a 10-year risk of CVD higher than 20%.

Hernandez D et al (2013)[15] conducted a cross sectional study in a representative sample of 2270 adults, 18 – 80 years, from Malaga (Spain) in order to determine HbA1c cut-off points for chronic kidney disease (CKD) and CVD. The authors showed that known DM was significantly associated with CKD, CVD, or both and that HbA1c levels were independently related to clinical endpoints after adjustment for traditional risk factors. However, when both known diabetes and HbA1c levels were introduced in the same model, DM was not significantly associated with CKD nor CVD, suggesting that significant associations between diabetes and CVD or CKD was mediated by HbA1c concentration, regardless of diabetic status.

Krishnan S et al (2011)[16] examined the presence of cardiovascular risk factors in 66 teenagers (13-20 years) with normal weight or overweight, both with and without type 1 diabetes (T1D). This study hypothesized if teenagers with T1D had a worse CV risk profile than those without T1D, and if there was a synergic or additive effect of overweight status and T1D on CV

risk profile. The authors found that T1D was not associated with higher cardiovascular risk profile and had consistently and paradoxically higher HDL-C levels (p=0.023) than non-T1D patients regardless of their overweight status. Also statistically significant adverse effect of diabetes on arterial compliance was not observed nor interaction between diabetes and overweight status. One limitation of this study is that only children with controlled T1D were included.

Studies giving no straight answer to the question "is diabetes a cardiovascular disease equivalent?"

In a case-control study, Deo RK et al (2008)[17] looked at the association between HbA1c levels and CVE, namely MI and stroke. 50 consecutive diabetic patients admitted in wards with CVE were included (25 with and 25 with stroke); 50 diabetic patients without CVE were taken as control. The authors showed that among patients with CVE and no CVE, the difference between levels of HbA1c was statistically significant (p=0.017). For MI, level of HbA1c was statistically significant (p=0.018) while for stroke, level of HbA1c was not significant. Likewise mean blood glucose also predicted CVE (p=0.006), MI (p=0.006) but not stroke. Fasting plasma glucose as well as postprandial plasma glucose also significantly predicted CVE (p=0.024 and 0.019, respectively).

van der Heijden AAWA et al (2009)[18] used prospective data from 1482 people (50-75 years), who participated in the Hoorn Study in order to validate and compare results from the Framingham, SCORE, and UKPDS risk functions in predicting CHD risk of individuals with normal glucose tolerance (NGT), intermediate hyperglycaemia (impaired glucose tolerance and/or IFG), and DM (screening-detected and previously known DM). The discriminatory ability of models was evaluated by calculating area under the receiver operating characteristic curve (AUROC); discriminatory power was graded low (AUROC 0.5-0.7), moderate (AUROC 0.7-0.9) or high (AUROC >0.9). The authors verified that Framingham and UKPDS risk functions overestimated the actual observed CHD incidence rate in all subgroups. The Framingham algorithm had low ability to discriminate the first CHD in NGT and intermediate hyperglycaemia groups (AUROC 0.68 and 0.60, respectively) and moderate discrimination ability in screening-

detected diabetes group (AUROC 0.74). The UKPDS function had moderate capacity to identify those with high risk for a first CHD event in NGT, intermediate hyperglycaemia and screening-detected diabetes subgroups (AUROC 0.71, 0.70and 0.75, respectively) but low ability when screening-detected and known diabetes were combined (AUROC 0.66). The SCORE algorithm for prediction of fatal CHD had a moderate ability in all subgroups. It was also verified that Framingham and UKPDS risk functions - designed to estimate first CHD in the general population and the diabetic population, respectively - performed better in estimating fatal CHD than the SCORE risk function.

In a case-control study, Gerstein HC et al (2010)[19] evaluated the relationship between HbA1c levels in MI patients and controls who participated in the INTERHEART study; 15152 MI patients who were admitted within 24 hours of their first acute MI and 14820 controls were included. The authors observed that a 1% increase in HbA1c was associated with a 40% higher odds of MI after controlling for age, sex and region alone, and a 19% higher odds after adjusting for the risk factors used (age, sex and region, diabetes, hypertension, current smoking, physical activity ≥ 4 hours/week, daily fruit and vegetable intake, alcohol intake, abdominal obesity, BMI, apoB/apoA). The importance of dysglycaemia as a risk factor for MI in the general population is further highlighted by an association between an HbA1c ≥5.4% and a 22% higher odds of MI, after adjusting for the risk factors used this study. It was also observed a 25% higher odds of MI in people with no previous diabetes and a 18% higher odds in people without previous diabetes history and an HbA1c<6.5% further emphasising the relevance of these findings to the general population. The authors concluded that HbA1c was an independent risk factor for MI in the presence of every other independent cardiovascular risk factor and self-reported diabetes underestimates the association between dysglycaemia and cardiovascular risk.

In a 15-year prospective cohort study, Wang H et al (2011)[20] followed 4549 American Indian adults, between 45-74 years, recruited from Strong Heart Study (1989–1991). Data from 3,850 individuals with baseline measurements of FPG and HbA1C and no prevalent CVD were analysed; 1,386 had known diabetes. This study showed that newly diagnosed diabetes via HbA1c ≥6.5% vs. non-diabetic patients was an independent CVD risk factor (HR 1.50) but not with CHD

(HR 1.43); previously known DM vs. non-diabetic patients had greater HR (2.52); Newly diagnosed diabetes via FPG ≥126 mg/dL vs FPG <100 mg/dL was also independent associated to CVD events (adjusted HR 2.52 [95% CI: 2.06-3.08]). Flat linear relations were observed between HbA1c and CVD and CHD in individuals without diabetes, with no suggestion of an inflection point at any HbA1c value. Comparing HbA1c and FPG in prediction models for CVD, HbA1c and as FPG were significant independent predictors (HR= 1.08 and 1.07, respectively) in subjects without known diabetes; in known diabetics, neither HbA1c nor FPG were significant independent predictors. However, no significant increase of CVD risk across HbA1c categories was shown within the pre-diabetic range after adjustment for known CVD risk factors.

Babar GS et al (2011)[21] hypothesized that children with T1D would manifest early signs of abnormal vascular homeostasis, endothelial dysfunction, increased carotid intima-media thickness (c-IMT), and elevated circulating markers of inflammation. Endothelial function was determined by percentage of flow mediated dilatation (FMD%) of the brachial artery. 21 children with T1D, aged 8.5±0.3 years (diabetes duration: 4.3±0.4 years), recruited from the Children's Hospital of Wisconsin Diabetes Clinic were included and compared with a 15 group-matched healthy siblings (aged 7.6±0.3 years). The authors verified positive correlation between FMD% and HbA1c (r=0.47, p=0.033) and FMD% and 2 week-glucose variability (r=0.50, p=0.021), adjusted for diabetes duration. However, no correlation between FMD% and HbA1c and 2 week-glucose variability among control subjects was found. These data suggest the presence of adverse changes in vascular homeostasis in preadolescent children with T1D during the earliest stages of their life.

Bozorgmanesh M et al (2012)[22] followed for a mean period of 8.6 years, 6331 patients with no CVD at baseline, aged >30 years, recruited from Tehran Lipid and Glucose Study, a population based prospective study. The aim of this study was to quantify CVD burden and all-cause mortality attributable to self-reported (SRDM) and screen-detected (SDDM) DM. During the follow-up period 447 CVE were registered (387 CHD events; 209 deaths). Comparing with non-diabetics, SRDM and SDDM were associated with CVD, CHD and all-cause mortality. Between SRDM and SDDM there was no significant difference of CVD or all-cause mortality;

however SRDM conferred 50% risk increase in CHD, when compared to SDDM (relative hazard ratio (RRR) 1.48, 95% CI 1.06-2.08). Amongst men, those with SDDM only had increased RRR for all-cause mortality (RRR 2.72) which translated to a population attributable risk fraction (PAF) of 10.1%. Amongst women, SDDM was associated with CVD (RRR 2.33) and CHD (RRR 2.31) but not with all-cause mortality (RRR 1.11), which translated to a PAF of 9.3% and 8.8% for CVD and CHD events.

In this retrospective study, Kato K et al (2012)[23] selected 98 patients who underwent 3-vessel optical coherence tomography (OCT) from the Massachusetts General Hospital OCT Registry and compared characteristics of non-culprit plaques between DM and non-DM patients. The authors showed that non-culprit plaques in patients with DM had a wider lipid arc (p=0.001), a longer lipid length (p=0.001), a larger lipid index (p<0.001), and a higher prevalence of calcification (p=0.034), and thrombus (p=0.047). DM patients were divided into 2 groups based on HbA1c level (HbA1c≤7.9% and HbA1c ≥8%), with no significant differences in treatment modality. When compared to DM with HbA1c ≤ 7.9% and non-DM patients, those with HbA1c ≥8% had non-culprit plaques with higher prevalence of thin-cap fibroatheroma (p=0.043 vs. HbA1c ≤ 7.9%; p=0.037 vs. non-DM patients) and macrophage infiltration (p=0.024 vs. HbA1c ≤ 7.9%; p=0.042 vs. non-DM patients), and thinner fibrous cap (p=0.035 vs. HbA1c ≤ 7.9%; p=0.004 vs. non-DM patients). When comparing non-DM patients and diabetics with HbA1c ≤ 7.9%, only longer lipid length (p=0.039) and a larger lipid index (p<0.042) were significant diferent. This results suggest more vulnerability in their coronary plaques in patients with poorly controlled DM.

Zoungas S et al (2012)[24] aimed to investigate the relationship between HbA1c and the risks of vascular complications and death in T2D patients. 11140 patients, age > 55 years, with at least one additional risk factor for CVD, were randomised to intensive or standard glucose control in the ADVANCE trial. In this randomized clinical trial a non-linear relationship between HbA1c levels and the risk of macrovascular events, all cause death and microvascular events was shown in overall population. Estimates for these risk associations were: macrovascular disease 6.57, all cause death 6.54 and microvascular disease 6.14. The authors concluded that HbA1c threshold

for macrovascular disease and all cause death is 6.5% to 7.0%, and for microvascular disease 6.0% to 6.5%. Authors also shown that for every 1% increase in HbA1c above these thresholds there was a 38% higher risk of macrovascular events and all cause death and a 40% higher risk of microvascular events. Below these thresholds there was no association between HbA1c levels and these three outcomes. Similar results were found in standard glucose control and intensive glucose control groups.

Eskesen K et al (2013)[25] included 5127 individuals (597 diabetics; 4530 non-diabetics) from the Danish general population, followed for 10 years in order to investigate the relationships between HbA1c, CVD, DM and all-cause mortality. During follow-up of up there were 732 deaths, 592 CVE and 61 cases of incident DM. The authors demonstrated that in the non-diabetic population HbA1c levels were significantly associated with incident fatal and nonfatal CVE in both univariate (HR 1.38; p=0.004) and multivariate analyses (HR 1.31; p=0.018). In the diabetic population, there was a non-significant trend towards an association between HbA1c and incident fatal and nonfatal CVE both in univariate and multivariate analyses. There was no significant association with development of macrovascular complications or all-cause mortality with HbA1c in these subjects.

Reviews

Echouffo-Tcheugui JB et al (2011)[26] aimed in this review to examine the usefulness of CVD risk models in patients with DM. The authors reviewed studies comparing the discriminative power of major cardiovascular risk factors, single or combined, in individuals with and without DM, for major cardiovascular outcomes. They concluded that CVD risk is not uniformly distributed in diabetics, rather it follows a gradient, thus the need for estimation of global CVD risk in these patients with improved and more refined tools to evaluate CVD risk in diabetic population.

Pistrosch F et al (2011)[27] questioned if hyperglycaemia was a cardiovascular risk factor. In this review the authors exposes the pathophysiological aspects of acute and chronic hyperglycaemia, their treatment and the relationship between hyperglycaemia and its treatment

with CVE. The authors concluded that hyperglycaemia is a CVD risk factor for patients with T2D and the treatment might reduce CVE and mortality if initiated early, if hypoglycaemia is avoided and if individualized therapeutic regimens are applied.

Wang CC and Reusch JE (2012)[28] in this review exposes the role of diabetes in atherosclerosis and cardiac dysfunction, as well as the evidence in controlling other CV risk factors such as high blood pressure, dyslipidaemia and albuminuria. The authors conclude that though there is a link between glycaemic control and the development of CVD there are numerous confounding factors, such as dyslipidaemia, obesity and high blood pressure, recommending multifaced approaches to reduce global cardiovascular risk.

Saely CH and Drexel H (2013)[29] questioned if T2D was a CHD risk equivalent. In this review, the author presented 9 studies that favoured diabetes as a CHD risk equivalent and 8 that refuted this finding. 8 articles, however, revealed a more complex interaction between DM and CVD risk, though pointing that DM *per se* is not a CVD risk equivalent. They concluded that these differences in literature are due to the fact that patients with diverse clinical background are often put together in the same group, for example, not all DM patients have history of CHD nor being asymptomatic excludes subclinical CVD, which can lead to patients being erroneously put together in the same primary prevention groups.

Sattar N (2013)[30] in this review compares Haffner's hypothesis with the newer findings and respective clinical implications. He states that: (a) diabetes is not a CHD risk equivalent at diagnosis nor in those with short duration of disease (<10 years); (b) risk levels approached CHD risk equivalence after diabetes duration ≥ 10 years or in those with proteinuria or CKD; (c) diabetics with existing CHD have an excess vascular risk comparing with those with CHD but without diabetes; (d) statin therapy might not be adequate for some patients.

This literature review from the last 5 years has shown that the paradigm of DM as a CVD equivalent has been changing, making room for a new perspective: diabetes *per se* should not be considered a risk equivalent[29]. FPG and HbA1C levels and duration of the disease are intrinsic to DM itself, thus being important confounders. Also patients are not equal and, therefore, not all

diabetics have history of CVD nor all patients with CVD suffer from DM.[29] Most importantly, being asymptomatic does not exclude the presence of subclinical CVD[29].

Sometimes patients with different CV risk are grouped in the same prevention cohort[29], meaning that some patients are undertreated and others are overtreated with risk modifier drugs, namely statins[30]. The use of these drugs should be prudent not to mistreat patients. Large population based studies are needed to create cut-off points and refine or create novel individualized risk assessment tools, using FPG and HbA1C levels and duration of disease instead of presence or absence of DM[12, 19, 23, 25].

In addition, more studies are required to investigate T1D population since the majority of studies cited focus on T2D or use non-discriminatory diabetic populations. The two articles found[16, 21] on T1D are not concordant.

Conclusions

The relationship between DM and CVD risk is a complex and since Haffner et al[4] in 1998, the paradigm that diabetes is a CVD risk equivalent has been changing. DM *per se* should not be considered a CVD risk equivalent and risk assessment tools should focus on parameters like HbA1C levels, FPG levels and duration of disease. This change in the paradigm has clinical implications, for example, restricting the use of statins in lower risk groups.

Population based studies are required in order to establish cut points for the parameters presented, ameliorate risk assessment in diabetic patients and evaluate the use of cardiovascular risk modifying drugs. In addition, more studies are required to study T1D population.

Bibliography

1. Howard BV, Best LG, Galloway JM, et al. Coronary heart disease risk equivalence in diabetes depends on concomitant risk factors. Diabetes Care. 2006;29(2):391-7.

2. Noble E, Melling J, Shoemaker K, et al. Innovation to reduce cardiovascular complications of diabetes at the intersection of discovery, prevention and knowledge exchange. Can J Diabetes. 2013;37(5):282-93.

3. Franco OH, Steyerberg EW, Hu FB, et al. Associations of diabetes mellitus with total life expectancy and life expectancy with and without cardiovascular disease. Arch Intern Med. 2007;167(11):1145-51.

4. Haffner SM, Lehto S, Ronnemaa T, et al. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339(4):229-34.

5. Juutilainen A, Lehto S, Ronnemaa T, et al. Type 2 diabetes as a "coronary heart disease equivalent": an 18-year prospective population-based study in Finnish subjects. Diabetes Care. 2005;28(12):2901-7.

6. Whiteley L, Padmanabhan S, Hole D, et al. Should diabetes be considered a coronary heart disease risk equivalent?: results from 25 years of follow-up in the Renfrew and Paisley survey. Diabetes Care. 2005;28(7):1588-93.

7. Evans JM, Wang J, Morris AD. Comparison of cardiovascular risk between patients with type 2 diabetes and those who had had a myocardial infarction: cross sectional and cohort studies. BMJ (Clinical research ed). 2002;324(7343):939-42.

8. Lee CD, Folsom AR, Pankow JS, et al. Cardiovascular events in diabetic and nondiabetic adults with or without history of myocardial infarction. Circulation. 2004;109(7):855-60.

9. Buyken AE, von Eckardstein A, Schulte H, et al. Type 2 diabetes mellitus and risk of coronary heart disease: results of the 10-year follow-up of the PROCAM study. European journal of cardiovascular prevention and rehabilitation : official journal of the European Society

of Cardiology, Working Groups on Epidemiology & Prevention and Cardiac Rehabilitation and Exercise Physiology. 2007;14(2):230-6.

10. Bulugahapitiya U, Siyambalapitiya S, Sithole J, et al. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med. 2009;26(2):142-8.

11. Berry C, Noble S, Gregoire JC, et al. Glycaemic status influences the nature and severity of coronary artery disease. Diabetologia. 2010;53(4):652-8.

12. Cano JF, Baena-Diez JM, Franch J, et al. Long-term cardiovascular risk in type 2 diabetic compared with nondiabetic first acute myocardial infarction patients: a population-based cohort study in southern Europe. Diabetes Care. 2010;33(9):2004-9.

13. Saely CH, Aczel S, Koch L, et al. Diabetes as a coronary artery disease risk equivalent: before a change of paradigm? European Journal of Cardiovascular Prevention & Rehabilitation. 2010;17(1):94-9.

14. Paynter NP, Mazer NA, Pradhan AD, et al. Cardiovascular Risk Prediction in Diabetic Men and Women Using Hemoglobin A(1c) vs Diabetes as a High-Risk Equivalent. Archives of Internal Medicine. 2011;171(19):1712-8.

15. Hernandez D, Espejo-Gil A, Bernal-Lopez MR, et al. Association of HbA1c and cardiovascular and renal disease in an adult Mediterranean population. BMC Nephrology. 2013;14(1).

16. Krishnan S, Copeland KC, Bright BC, et al. Impact of Type 1 Diabetes and Body Weight Status on Cardiovascular Risk Factors in Adolescent Children. Journal of Clinical Hypertension. 2011;13(5):351-6.

17. Deo RK, Karki P, Sharma SK, et al. Association of cardiovascular events with glycosylated haemoglobin in diabetic patients. Kathmandu University Medical Journal. 2008;6(24):476-85.

18. van der Heijden AAWA, Ortegon MM, Niessen LW, et al. Prediction of Coronary Heart Disease Risk in a General, Pre-Diabetic, and Diabetic Population During 10 Years of Follow-up: Accuracy of the Framingham, SCORE, and UKPDS Risk Functions The Hoorn Study. Diabetes Care. 2009;32(11):2094-8.

19. Gerstein HC, Islam S, Anand S, et al. Dysglycaemia and the risk of acute myocardial infarction in multiple ethnic groups: An analysis of 15,780 patients from the INTERHEART study. Diabetologia. 2010;53(12):2509-17.

20. Wang H, Shara NM, Lee ET, et al. Hemoglobin A(1c), Fasting Glucose, and Cardiovascular Risk in a Population With High Prevalence of Diabetes The Strong Heart Study. Diabetes Care. 2011;34(9):1952-8.

21. Babar GS, Zidan H, Widlansky ME, et al. Impaired endothelial function in preadolescent children with type 1 diabetes. Diabetes Care. 2011;34(3):681-5.

22. Bozorgmanesh M, Hadaegh F, Sheikholeslami F, et al. Cardiovascular risk and all-cause mortality attributable to diabetes: Tehran lipid and glucose study. J Endocrinol Invest. 2012;35(1):14-20.

23. Kato K, Yonetsu T, Kim S-J, et al. Comparison of Nonculprit Coronary Plaque Characteristics Between Patients With and Without Diabetes A 3-Vessel Optical Coherence Tomography Study. Jacc-Cardiovascular Interventions. 2012;5(11):1150-8.

24. Zoungas S, Chalmers J, Ninomiya T, et al. Association of HbA 1c levels with vascular complications and death in patients with type 2 diabetes: Evidence of glycaemic thresholds. Diabetologia. 2012;55(3):636-43.

25. Eskesen K, Jensen MT, Galatius S, et al. Glycated haemoglobin and the risk of cardiovascular disease, diabetes and all-cause mortality in the Copenhagen City Heart Study. Journal of Internal Medicine. 2013;273(1):94-101.

26. Echouffo-Tcheugui JB, Ogunniyi MO, Kengne AP. Estimation of absolute cardiovascular risk in individuals with diabetes mellitus: rationale and approaches. ISRN cardiology. 2011;2011:242656.

27. Pistrosch F, Natali A, Hanefeld M. Is Hyperglycemia a Cardiovascular Risk Factor? Diabetes Care. 2011;34:S128-S31.

28. Wang CC, Reusch JE. Diabetes and cardiovascular disease: changing the focus from glycemic control to improving long-term survival. The American journal of cardiology. 2012;110(9 Suppl):58B-68B.

29. Saely CH, Drexel H. Is type 2 diabetes really a coronary heart disease risk equivalent? Vascul Pharmacol. 2013;59(1-2):11-8.

30. Sattar N. Revisiting the links between glycaemia, diabetes and cardiovascular disease. Diabetologia. 2013;56(4):686-95.

Images subtitles

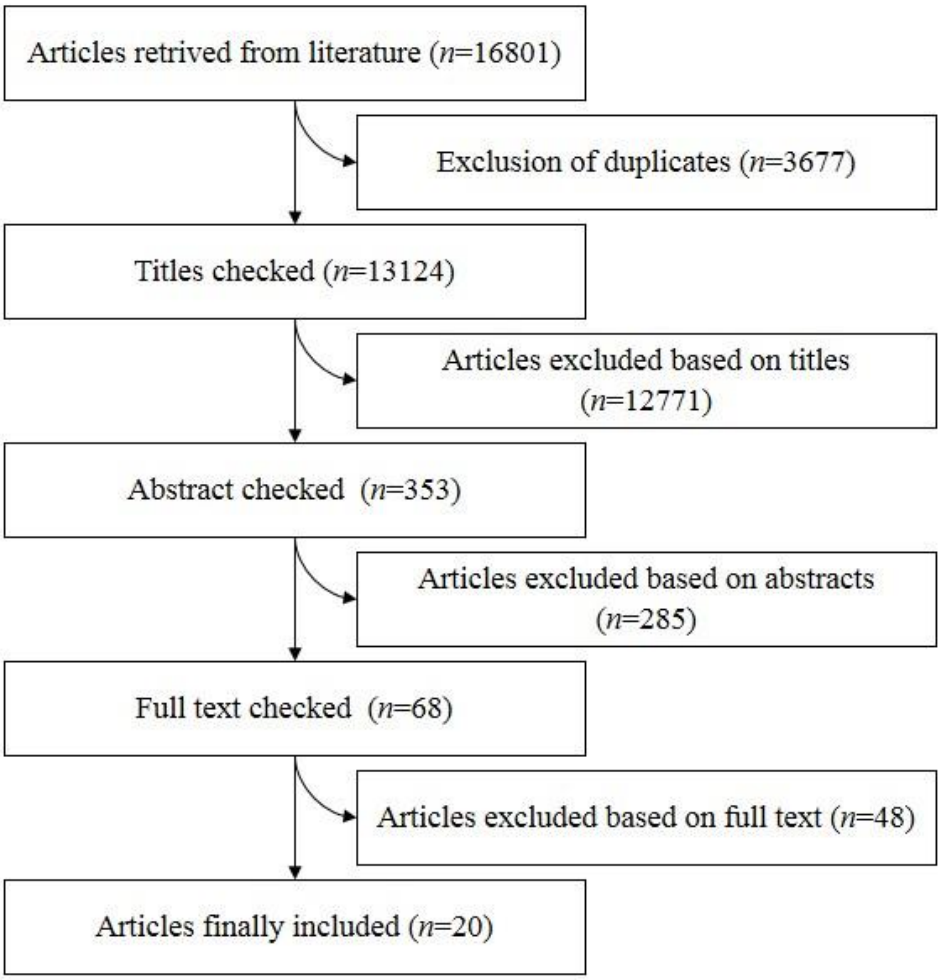
Fig.1 – Flow of identification of included studies.

Table 1 - Overview of included articles.

Authors	Year of Publication	Type of study	Favors diabetes as a CVD risk equivalent	Diabetes mellitus
Deo RK, Karki P, Sharma SK, et al.	2008	Case control	0	NE
van der Heijden AAWA, Ortegon MM, Niessen LW, et al.	2009	Prospective cohort	0	DMT2
Berry C, Noble S, Gregoire JC, et al.	2010	Clinical trial	+	DMT2
Cano JF, Baena-Diez JM, Franch J, et al.	2010	Prospective cohort	-	DMT2
Gerstein HC, Islam S, Anand S, et al.	2010	Case control	0	NE
Saely CH, Aczel S, Koch L, et al.	2010	Prospective cohort	-	DMT2
Babar GS, Zidan H, Widlansky ME, et al.	2011	Cross sectional	0	DMT1
Echouffo-Tcheugui JB, Ogunniyi MO, Kengne AP.	2011	Review	0	NE
Krishnan S, Copeland KC, Bright BC, et al.	2011	Cross sectional	-	DMT1
Paynter NP, Mazer NA, Pradhan AD, et al.	2011	Prospective cohort	-	NE
Pistrosch F, Natali A, Hanefeld M.	2011	Review	0	NE
Wang H, Shara NM, Lee ET, et al.	2011	Prospective cohort	0	NE
Bozorgmanesh M, Hadaegh F, Sheikholeslami F, et al.	2012	Prospective cohort	0	NE

Kato K, Yonetsu T, Kim S-J, et al.	2012	Retrospective	0	NE
Wang CC, Reusch JE.	2012	Review	0	NE
Zoungas S, Chalmers J, Ninomiya T, et al.	2012	Randomized clinical trial	0	DMT2
Eskesen K, Jensen MT, Galatius S, et al.	2013	Prospective cohort	0	NE
Hernandez D, Espejo-Gil A, Bernal-Lopez MR, et al.	2013	Cross sectional	-	NE
Saely CH, Drexel H.	2013	Review	0	NE
Sattar N.	2013	Review	-	NE

+ - Suports the hipothesis that diabetes is a cardiovascular disease equivalent. - - Refutes the hipothesis that diabetes is a cardiovascular disease equivalent. 0 – No straight answer is given to the question “is diabetes a cardiovascular disease equivalent?”. DMT1 – Data exclusively from patients with type 1 diabetes mellitus was quoted in the study or reviewed; DMT2 - Data exclusively from patients with type 2 diabetes mellitus was quoted in the study or reviewed; NE – It was not explicit if quoted data belonged to patients who suffered from type 1 or type 2 diabetes mellitus.


Articles retrived from literature (n=16801)
Exclusion of duplicates (n=3677)
Titles checked (n=13124)
Articles excluded based on titles (n=12771)
Abstract checked (n=353)
Articles excluded based on abstracts (n=285)
Full text checked (n=68)
Articles excluded based on full text (n=48)
Articles finally included (n=20)

Agradecimentos

Agradeço a todos os que, mesmo não estando envolvidos directamente na elaboração desta tese, me ajudaram de uma maneira ou de outra: agradeço ao Luís Manuel Ferreira Pinto por todas as dicas e sugestões dadas; agradeço a todos os meus amigos e colegas que, de uma forma ou de outra, suportaram os meus devaneios; agradeço aos meus pais, madrinha, e primos por todo apoio e força dados.

Normas de publicação da Revista Portuguesa de Cardiologia

A Revista Portuguesa de Cardiologia, órgão oficial da Sociedade Portuguesa de Cardiologia, é uma publicação científica internacional destinada ao estudo das doenças cardiovasculares.

Publica artigos em português na sua edição em papel e em português e inglês na sua edição online, sobre todas as áreas da Medicina Cardiovascular. Se os artigos são publicados apenas em inglês, esta versão surgirá simultaneamente em papel e online. Inclui regularmente artigos originais sobre investigação clínica ou básica, revisões temáticas, casos clínicos, imagens em cardiologia, comentários editoriais e cartas ao editor. Para consultar as edições online deverá aceder através do link www.revportcardiol.org.

Todos os artigos são avaliados antes de serem aceites para publicação por peritos designados pelos Editores (peer review). A submissão de um artigo à Revista Portuguesa de Cardiologia implica que este nunca tenha sido publicado e que não esteja a ser avaliado para publicação noutra revista.

Os trabalhos submetidos para publicação são propriedade da Revista Portuguesa de Cardiologia e a sua reprodução total ou parcial deverá ser convenientemente autorizada. Todos os autores deverão enviar a Declaração de Originalidade, conferindo esses direitos à RPC, na altura em que os artigos são aceites para publicação.

Envio de manuscritos

Os manuscritos para a Revista Portuguesa de Cardiologia são enviados através do link http://www.ees.elsevier.com/repc. Para enviar um manuscrito, é apenas necessário aceder ao referido link e seguir todas as instruções que surgem.

Responsabilidades Éticas

Os autores dos artigos aceitam a responsabilidade definida pelo Comité Internacional dos Editores das Revistas Médicas (consultar www.icmje.org).

Os trabalhos submetidos para publicação na Revista Portuguesa de Cardiologia devem respeitar as recomendações internacionais sobre investigação clínica (Declaração de Helsínquia da Associação Médica Mundial, revista recentemente) e com animais de laboratório (Sociedade Americana de Fisiologia). Os estudos aleatorizados deverão seguir as normas CONSORT.

Informação sobre autorizações

A publicação de fotografias ou de dados dos doentes não devem identificar os mesmos. Em todos os casos, os autores devem apresentar o consentimento escrito por parte do doente que autorize a sua publicação, reprodução e divulgação em papel e na Revista Portuguesa de Cardiologia. Do mesmo modo os autores são responsáveis por obter as respectivas autorizações para reproduzir na Revista Portuguesa de Cardiologia todo o material (texto, tabelas ou figuras) previamente publicado. Estas autorizações devem ser solicitadas ao autor e à editora que publicou o referido material.

Conflito de interesses

Cada um dos autores deverá indicar no seu artigo se existe ou não qualquer tipo de Conflito de Interesses.

Declaração de originalidade

O autor deverá enviar uma declaração de originalidade. Ver anexo I

Protecção de dados

Os dados de carácter pessoal que se solicitam vão ser tratados num ficheiro automatizado da Sociedade Portuguesa de Cardiologia (SPC) com a finalidade de gerir a publicação do seu artigo na Revista Portuguesa de Cardiologia (RPC). Salvo indique o contrário ao enviar o artigo, fica expressamente autorizado que os dados referentes ao seu nome, apelidos, local de trabalho e correio electrónico sejam publicados na RPC, bem como no portal da SPC (www.spc.pt) e no portal online www.revportcardiol.org, com o intuito de dar a conhecer a autoria do artigo e de possibilitar que os leitores possam comunicar com os autores.

INSTRUÇÕES AOS AUTORES

Todos os manuscritos deverão ser apresentados de acordo com as normas de publicação. Pressupõe-se que o primeiro autor é o reponsável pelo cumprimento das normas e que os restantes autores conhecem, participam e estão de acordo com o conteúdo do manucrito.

1. Artigos Originais

Apresentação do documento:

- Com espaço duplo, margens de 2,5 cm e páginas numeradas.
- Não deverão exceder 5.000 palavras, contadas desde a primeira à última página, excluindo as tabelas.
- Consta de dois documentos: primeira página e manuscrito
- O manuscrito deve seguir sempre a mesma ordem: a) resumo estruturado em português e palavras-chave; b) resumo estruturado em inglês e palavras-chave; c) quadro de abreviaturas em português e em inglês; d) texto; e) bibliografia; f) legendas das figuras; g) tabelas (opcional) e h) figuras (opcional)-

Primeira página

Título completo (menos de 150 caracteres) em português e em inglês.

Nome e apelido dos autores pela ordem seguinte: nome próprio, seguido do apelido (pode conter dois nomes)

Proveniência (Serviço, Instituição, cidade, país) e financiamento caso haja.

Endereço completo do autor a quem deve ser dirigida a correspondência, fax e endereço electrónico.

Faz-se referência ao número total de palavras do manuscrito (excluindo as tabelas).

Resumo estruturado

O resumo, com um máximo de 250 palavras, está dividido em quatro partes: *a)* Introdução e objectivos; *b)* Métodos; *c)* Resultados e *d)* Conclusões.

Deverá ser elucidativo e não inclui referências bibliográficas nem abreviaturas (excepto as referentes a unidades de medida).

Inclui no final três a dez palavras-chave em português e em inglês. Deverão ser preferencialmente seleccionadas a partir da lista publicada na Revista Portuguesa de Cardiologia, oriundas do Medical Subject

Headings (MeSH) da National Libray of Medicine, disponível em: www.nlm.nihgov/mesh/meshhome.html.

O resumo e as palavras-chave em inglês devem ser apresentados da mesma forma.

Texto

Deverá conter as seguintes partes devidamente assinaladas: *a)* Introdução; *b)* Métodos; *c)* Resultados; *d)* Discussão e *e)* Conclusões. Poderá utilizar subdivisões adequadamente para organizar cada uma das secções.

As abreviaturas das unidades de medida são as recomendadas pela RPC (ver Anexo II).

Os agradecimentos situam-se no final do texto.

Bibliografia

As referências bibliográficas deverão ser citadas por ordem numérica no formato 'superscript', de acordo com a ordem de entrada no texto.

As referências bibliográficas não incluem comunicações pessoais, manuscritos ou qualquer dado não publicado. Todavia podem estar incluídos, entre parêntesis, ao longo do texto.

São citados abstracts com menos de dois anos de publicação, identificando-os com [abstract] colocado depois do título.

As revistas médicas são referenciadas com as abreviaturas utilizadas pelo Index Medicus: List of Journals Indexed, tal como se publicam no número de Janeiro de cada ano. Disponível em: http://www.ncbi.nlm.nih.gov/entrez/citmatch_help.html#JournalLists.

O estilo e a pontuação das referências deverão seguir o modelo Vancouver 3.

Revista médica: Lista de todos os autores. Se o número de autores for superior a três, incluem-se os três primeiros, seguidos da abreviatura latina et al. Exemplo:

17. Sousa PJ, Gonçalves PA, Marques H et al. Radiação na AngioTC cardíaca; preditores de maior dose utilizada e sua redução ao longo do tempo. Rev Port cardiol, 2010; 29:1655-65

Capítulo em livro: Autores, título do capítulo, editores, título do livro, cidade, editora e páginas. Exemplo:

23. Nabel EG, Nabel GJ. Gene therapy for cardiovascular disease. En: Haber E, editor. Molecular cardiovascular medicine. New York: Scientific American 1995. P79-96.

Livro: Cite as páginas específicas. Exemplo:

30. Cohn PF. Silent myocardial ischemia and infarction. 3rd ed. New York: Mansel Dekker; 1993. P. 33.

Material electrónico: Artigo de revista em formato electrónico. *Exemplo:*

Abood S. Quality improvement initiative in nursing homes: the ANA acts it an advisory role. Am J Nurs. [serie na internet.] 2002 Jun citado 12 Ago 2002:102(6): [aprox. 3] p. Disponível em: http://www.nursingworld.org/AJN/2002/june/Wawatch.htm

. A Bibliografia será enviada como texto regular, nunca como nota de rodapé. Não se aceitam códigos específicos dos programas de gestão bibliográfica.

1. Figuras

As figuras correspondentes a gráficos e desenhos são enviadas no formato TIFF ou JPEG de preferência, com uma resolução nunca inferior a 300 dpi e utilizando o negro para linhas e texto. São alvo de numeração árabe de acordo com a ordem de entrada no texto.

- A grafia, símbolos, letras, etc, deverão ser enviados num tamanho que, ao ser reduzido, os mantenha claramente legíveis. Os detalhes especiais deverão ser assinalados com setas contrastantes com a figura.
- As legendas das figuras devem ser incluídas numa folha aparte. No final devem ser identificadas as abreviaturas empregues por ordem alfabética.
- As figuras não podem incluir dados que dêem a conhecer a proveniência do trabalho ou a identidade do paciente. As fotografias das pessoas devem ser feitas de maneira que estas não sejam identificadas ou incluir-se-á o consentimento por parte da pessoa fotografada.

Tabelas

São identificadas com numeração árabe de acordo com a ordem de entrada no texto.

Cada tabela será escrita a espaço duplo numa folha aparte.

- Incluem um título na parte superior e na parte inferior são referidas as abreviaturas por ordem alfabética.
- O seu conteúdo é auto-explicativo e os dados que incluem não figuram no texto nem nas figuras.

2. Cartas ao Editor

Devem ser enviadas sob esta rubrica e referem-se a artigos publicados na Revista. Serão somente consideradas as cartas recebidas no prazo de oito semanas após a publicação do artigo em questão.

- Com espaço duplo, com margens de 2,5 cm.
- O título (em português e em inglês), os autores (máximo quatro), proveniência, endereço e figuras devem ser especificados de acordo com as normas anteriormente referidas para os artigos originais.
- Não podem exceder as 800 palavras.
- Podem incluir um número máximo de duas figuras. As tabelas estão excluídas.

3. Casos Clínicos

Devem ser enviados sob esta rubrica.

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder 10 palavras

Os autores (máximo oito) proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.

O texto explicativo não pode exceder 3.000 palavras e contem informação de maior relevância. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.

Contêm um número máximo de 4 figuras e pode ser enviado material suplementar, como por exemplo vídeoclips.

4. Imagens em Cardiologia

- A espaço duplo com margens de 2,5 cm.
- O título (em português e em inglês) não deve exceder oito palavras
- Os autores (máximo seis), proveniência, endereço e figuras serão especificados de acordo com as normas anteriormente referidas para os artigos originais.
- O texto explicativo não pode exceder as 250 palavras e contem informação de maior relevância, sem referências bibliográficas. Todos os símbolos que possam constar nas imagens serão adequadamente explicados no texto.
- Contêm um número máximo de quatro figuras.

5. Material adicional na WEB

A Revista Portuguesa de Cardiologia aceita o envio de material electrónico adicional para apoiar e melhorar a apresentação da sua investigação científica. Contudo, unicamente se considerará para publicação o material electrónico adicional directamente relacionado com o conteúdo do artigo e a sua aceitação final dependerá do critério do Editor. O material adicional aceite não será traduzido e publicar-se-á electronicamente no formato da sua recepção.

Para assegurar que o material tenha o formato apropriado recomendamos o seguinte:

	Formato	Extensão	Detalhes
Texto	Word	.doc ou docx	Tamanho máximo 300 Kb
Imagem	JPG	.jpg	Tamanho máximo 10MB
Audio	MP3	.mp3	Tamanho máximo 10MB
Vídeo	WMV	.wmv	Tamanho máximo 30MB

Os autores deverão submeter o material no formato electrónico através do EES como arquivo multimédia juntamente com o artigo e conceber um título conciso e descritivo para cada arquivo.

Do mesmo modo, este tipo de material deverá cumprir também todos os requisitos e responsabilidades éticas gerais descritas nessas normas.

O Corpo Redactorial reserva-se o direito de recusar o material electrónico que não julgue apropriado.

ANEXO I

DECLARAÇÃO

Declaro que autorizo a publicação do manuscrito:

Ref.ª .....

Título .....

.....

.....

.....

do qual sou autor ou c/autor.

Declaro ainda que presente manuscrito é original, não foi objecto de qualquer outro tipo de publicação e cedo a inteira propriedade à Revista Portuguesa de Cardiologia, ficando a sua reprodução, no todo ou em parte, dependente de prévia autorização dos editores.

Nome dos autores:

.....

.....

.....

Assinaturas:

ANEXO II

Símbolos, abreviaturas de medidas ou estatística

Designação	Português	Inglês
Ampere	A	A
Ano	ano	yr
Centímetro quadrado	cm_2	cm_2
Contagens por minuto	cpm	cpm
Contagens por segundo	cps	cps
Curie	Ci	Ci
Electrocardiograma	ECG	ECG
Equivalente	Eq	Eq
Grau Celsius	°C	°C
Grama	g	g
Hemoglobina	Hb	Hb
Hertz	Hz	Hz
Hora	h	h
Joule	J	J
Litro	L ou L	l ou L
Metro	m	m
Minuto	min	min
Molar	M	M
Mole	mol	mol
Normal (concentração)	N	N
Ohm	Ω	Ω
Osmol	osmol	osmol
Peso	peso	WT
Pressão parcial de CO_2	pCO_2	pCO_2
Pressão parcial de O_2	pO_2	pO_2
Quilograma	kg	kg
Segundo	s	sec
Semana	Sem	Wk
Sistema nervoso central	SNC	CNS
Unidade Internacional	UI	IU
Volt	V	V
Milivolt	mV	mV
Volume	Vol	Vol
Watts	W	W
Estatística:		
Coeficiente de correlação	r	r
Desvio padrão (standard)	DP	SD
Erro padrão (standard) da média	EPM	SEM
Graus de liberdade	gl	df
Média	χ	χ
Não significativa	NS	NS
Número de observações	n	n
Probabilidade	p	p
Teste «t» de Student	teste t	t test